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Original Research

Could procalcitonin guide the use of antibiotics in acute exacerbation of chronic obstructive pulmonary disease?

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Abstract
Aim: Chronic Obstructive Pulmonary Disease (COPD) is predicted to become the third leading cause of death worldwide by 2030. Despite the fact that viral pathogens are play a major role in causing AECOPD, antibiotics are widely used in hospitals and cause various side effects. The purpose of this study is to understand whether procalcitonin levels can be used as a new guideline for antibiotic treatment in AECOPD.
Material and Methods: The study included 54 patients: 20 infectious AECOPD patients and 20 non-infectious AECOPD patients and 14 stable COPD controls. Standard treatment, antibiotics and systemic steroids have been given to the infectious COPD group for 10 days. Standard treatment and steroids have been given to the noninfectious group. Before and after treatment PCT was compared.
Results: In the infectious group, PCT level was above 0,25 pg/L. In the non-infectious group, procalcitonin level was 0,10- 0,25 pg/L. In the control group, procalcitonin level was below 0,1 pg/L. Accordingly, after 10 days, low procalcitonin levels were found in all groups.
Discussion: In our study, it was observed that procalcitonin levels decreased after antibiotic and steroid treatment in infectious AECOPD and after steroid treatment in non-infectious AECOPD. We conclude that a 0,25 pg/L level can be used as a threshold value, antibiotics should be started above 0,25 pg/L, and patients should be observed more closely as this level increased. We observed that after 7-10 days PCT level reduced to under 0.1 pg/L.

Keywords
Procalcitonin, COPD, Antibiotics, Acute Exacerbation, Biomarkers

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Introduction

COPD has been reported as the third leading cause of death worldwide in 2016, with around 3 million deaths annually and the incidence is predicted to increase each year until at least 2030 [1]. Exacerbations in chronic obstructive pulmonary disease (COPD) are defined in several ways, although many clinicians and researchers use the classic Anthonisen criteria [2]. Such criteria can lead to antibiotic and corticosteroid overuse, since they do not necessarily differentiate which patients are in need of such treatments, and in case of doubt, treatment will often be initiated, to avoid undertreating [3]. Research has shown that the overall prevalence of bacterial infection was approximately 50% in AECOPD patients, however, nearly 90% of hospitalized AECOPD patients were given antibiotics [4]. The overuse of antibiotics for respiratory infections is an important cause of multidrug resistance. Therefore, it is imperative to develop effective diagnostic tools to guide both corticosteroid and antibiotic treatment in lung patients and in patients with respiratory infections [5].

Procalcitonin (PCT) is a biomarker specific to bacterial pathogens, and the use of PCT-guided algorithms has demonstrated an ability to reduce antibiotic exposure in patients with pneumonia without negatively impacting clinical outcomes in randomized controlled studies.

In response to bacterial-induced cytokines, PCT is released ubiquitously into the bloodstream. Conversely, production is attenuated by cytokines released in response to viral infections [6].

In the patient care setting, serum PCT is measured and then applied clinically based on algorithms that use different thresholds to guide antibacterial initiation or for early discontinuation. The United States (US) Food and Drug Administration (FDA)-approved thresholds for these assays are as follows: antibiotics strongly discouraged if PCT < 0.1 μg·L−1, discouraged for serum levels between 0.1 and 0.25 μg·L−1, recommended for levels > 0.25 to 0.5 μg·L−1, and strongly recommended for levels > 0.5 μg·L−1 [7].

In our study, we aimed to assess the ability of PCT to distinguish between bacterial and nonbacterial causes of AECOPD and to understand how we can use PCT in the most effective way to guide the treatment.

Material and Methods

A total of 54 patients who were admitted to the Yedikule Chest Diseases Training and Research Hospital for AECOPD between January and June 2009 were enrolled in the study.

COPD patients were defined as patients who were 40 years or older with a history of ≥10 years, with dyspnea, chronic cough, biomass exposure, sputum and irreversible airway obstruction proven by spirometry.

The exclusion criteria were patients with symptoms other than COPD, with a psychiatric disorder, patients with extremely low immune function, asthma, those who admitted to the hospital for various reasons, who were treated with steroids or antibiotics in the last 3 weeks. There were 3 groups in the study: Group 1: AECOPD patients who had high Leukocytosis, CRP, sedimentation, high fever and pathogen, isolated from sputum. Group 2: non-infectious AECOPD patients who did not have high Leukocytosis, CRP, sedimentation and no pathogens isolated from sputum and Group 3: a stable COPD control group recruited in this study. Patients who were enrolled in the study have been evaluated according to Anthonisen Criteria and classified their exacerbations as severe, moderate and mild. On admission, in addition to anamnesis of patients, laboratory data were collected, including routine biochemical tests (urea, creatinine, total protein, alanine aminotransferase [ALT], aspartate aminotransferase [AST], LDH, CRP, erythrocyte sedimentation (ESR), spirometry and arterial blood pressure of oxygen [PaO2]. AECOPD patients were admitted to the hospital, and procalcitonin levels were measured. As for stable COPD patients, only PCT levels were measured and no additional treatment was given except for standard treatment, and they were not hospitalized. In determining Procalcitonin levels, Biomerieux, (France) ELISA technique was used.

The study protocol was approved by the ethics committee of Yedikule Chest Diseases Training and Research Hospital.

Statistical analysis

The ANOVA with Tukey HSD test was used to compare age, SFT, blood gas, leukocytes, CRP, total protein and procalcitonin in different groups. All categorical variables (sex, normal, pathologic, etc.) were compared using the Chi-square test. In addition, a comparison of the initial and control PCT was performed using the Wilcoxon test. $P<0.05$ indicated that the difference has statistical significance. SPSS Inc. released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc. was used for statistical analysis.

Results

In this study, a total of 55 patients were included in three groups: 20 patients in group 1, 24 patients in group 2 and 15 patients in group 3. One patient from group 1 and 4 patients from group 2 have been ruled out from study since a pathogen has been isolated from their sputum.

In group 1: the median age was 57± 10.86 (40-82) years, 17 were male and 3 were female patients. Four patients were followed in the hospital and 16 patients were followed as an outpatient. Two patients were in severe attack, 5 patients were moderate and 4 patients were mild. None of the patients required hospitalization in the intensive care unit. Nineteen patients were smokers, 1 patient was a non-smoker but had biomass exposure.

The pathogens isolated from the sputum of patients were Strep. Pneumonia in 14 patients, Klebsiella in 2 patients, Pseudomonas Aeroginosa in 1 patient, Acinetobacter in 1 patient, E. Coli in 1 patient, Proteus Mirabilis in 1 patient. Thirteen of the patients had radiological findings, and 3 of them had no findings. CRP was high in 19 patients and normal in 1 patient. Sedimentation was high in 18 patients and normal in 2 patients. Fifteen patients had leukocytosis and 5 of them were normal.

In group 2: the median age was 63.95± 13.07 (39-84) years, 16 were male and 4 were female patients. Three patients were followed in the hospital, and 17 patients were followed as an outpatient. Six patients were in severe attack, 7 patients were moderate and 7 patients were mild. None of the patients needed hospitalization in the intensive care unit. Eighteen patients were smokers, 2 female patients were non-smokers,

but had biomass exposure history. No pathogen was isolated from the sputum of the group 2 patients. Two patients had radiological findings,18 had no findings. CRP was high in 6 patients and normal in 14 patients. Sedimentation was high in 2 patients, normal in 18 patients. All 20 patients had normal leukocyte counts.

In Group 3: 14 patients were recruited with median age of 63.7± 19.86 (46-76) years, 13 were males and 1 was female. All 14 patients were smokers. There was no growth in the sputum culture and no radiological finding in any of the patients. In all patients CRP and sedimentation levels were normal. Group features are showed in Table 1.

There was no statistically significant difference between the groups in terms of smoking. The indication of radiological findings is statistically meaningful in infectious cases compared to non-infectious and stabile groups. Laboratory findings are illustrated in Table 2.

In infectious cases, CRP levels and leukocytosis frequency were significantly higher compared to non-infectious and stable group patients (p<0,001). In infectious cases, sedimentation level was significantly higher compared to non-infectious and stable group patients (p<0,001).

There was no statistically significant difference between the groups in terms of LDH, total protein values (p>0,05). In infectious cases, leukocyte level was significantly higher compared to non-infectious and stable group patients (p<0,001). Comparison of procalcitonin values is presented in Table 3.

In infectious cases, PCT level was significantly higher compared to non-infectious and stable group patients (p<0,001).

There was no statistically significant difference between the groups in terms of post-treatment PCT levels (p>0,05). In all groups, PCT levels were reduced significantly.

Table 1. Comparison of age, sex, smoking status, and radiological findings among three groups.

	GROUP 1 20	GROUP 2 20	GROUP 3 14	P
AGE	57 (10,86)	63,95 (13,07)	63,71 (9,86)	0,117
SEX	17 MALE, 3 FEMALE	16 MALE, 4 FEMALE	13 MALE, I FEMALE	0,583
SMOKING	19 SMOKER, I NON-SMOKER	18 SMOKER 2 NON-SMOKER	14 SMOKER	0,452
RADIOLOGICAL FINDINGS	13 have findings 7 none	2 have findings 18 none	14 none	0,000***

Table 2. Comparison of laboratory parameters among three groups.

	GROUP 1 20	GROUP 2 20	GROUP 3 14	P
CRP	1 normal, 19 high 75.49+70,ıı	14 normal, 6 high	14 normal 3,61+1,66	0,000***
SEDIMENTATION	2 normal, 18 high 62,80±23,75	18 normal, 2 high 21,10±14,74	14 normal	0
LEUKOCYTE	5 normal, 15 high	20 normal	14 normal	0,000***
LDH	159,85±55,19	143,30±20,93	145,50±18,36	0,738
TOTAL PROTEIN		7,51+0,46		0,976

Table 3. Comparison of procalcitonin levels pre- and post-treatment among three groups.

PROCALCITONIN	PRE-TREATMENT	POST-TREATMENT	P
GROUP 1	0,31±0,07	0,06+0,04	0,000
GROUP 2	0,22±0,05		0,000
GROUP 3	0,09±0,05	0,05±0,04	0,05
	0,000***	0,443	

Discussion

Patients with an acute exacerbation of COPD combined with respiratory failure develop a systemic inflammatory response, and an elevated PCT level is an indicator of oxidative stress and an inflammatory immune response in patients, providing an effective guide for stopping or starting antibiotics in patients with acute respiratory infections [8].

In order to test this theory, 3 groups of patients have been examined. 20 AECOPD patients who had pathogen isolated from their sputum and had high leukocytosis, CRP, sedimentation ; 20 non-infectious patients who had normal CRP, leukocytosis, sedimentation level, lastly as a control group, 14 stable COPD patients were examined. In addition to standard therapy, antibiotic and systemic corticosteroid therapies were given to infectious AECOPD patients for 10 days. As for non-infectious AECOPD patients, in addition to standard therapy, systemic corticosteroids were administered. At admission and after treatment, PCT levels were measured. In our study, we decided to administer antibiotics based on CRP, leukocytosis, radiological infiltration, purulent sputum, and bacterial pathogen abundance in sputum that leads us to think of a bacterial infection. Indeed, the PCT level of these cases was above 0.25 pg/L, compatible with the literature. Measuring PCT levels and detecting a level above 0.25 pg/L may be considered as a potential guide for antibiotic administration in AECOPD patients, but should be interpreted in conjunction with other clinical and laboratory findings to make informed treatment decisions. When we controlled the PCT level after 10 days in bacterial-infected acute attack patients, we observed that the PCT level reduced under 0.1 pg/L. Also, we observed that the PCT level dropped significantly after 10 days in non-infectious or nonbacterial infectious acute attack patients and stable COPD patients.

We detected that all infectious AECOPD patients with high PCT levels (>0.25 pg/L) were also in the severe attack group based on Anthonisen Group 1. In this context, the high PCT level can be used as a reference for the severity of the attacks. In our analysis, after administering antibiotics to the patients in Group 1, the PCT level dropped under 0.1 pg/L. The PCT level was in the range of 0.1-0.25 pg/L in the non-bacterial AECOPD group. Recently published results from prospective observational studies indicate that the evaluation of the dynamic changes in biomarker levels over time may give more reliable help in decision- making than absolute values [9]. It has been also concluded in the most recent review that PCT measurements approximately every 48 hours can lead to a reduction in antibiotics of at least 30%, without any obvious disadvantages; in fact, such a strategy reduces mortality and antibiotic-related side effects in patients with lower respiratory tract infections

(level 1A evidence), effects that seem likely also to apply to COPD patients [10]. We also came to the same result.

Conclusion

In our study, we found that the 0.25 pg/L cut-off value is in significant agreement with the literature, and as the value gets higher, the patient needs to be followed up more closely. Concurrently, PCT measurement could help prevent unnecessary and long antibiotic usage. Moreover, we concluded that antibiotic treatment could be discontinued if the PCT level falls below 0.1 pg/L after 7-10 days. Overall, the findings of this study indicate that PCT can play an important role in the management of AECOPD to reduce unnecessary antibiotic prescriptions.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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